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Relapse in the first three months postpartum in women with history of serious mental illness

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ABSTRACT

Background: Relapse of serious mental illness (psychotic and bipolar disorders; SMI) in the postpartum period is potentially devastating for mother and baby. There is limited evidence on whether medication in the perinatal period is protective against postpartum relapse for women with SMI particularly non-affective psychoses. We aimed to investigate risk factors for postpartum relapse, particularly the potential prophylactic effects of medication.

Methods: Using an anonymised resource of comprehensive electronic secondary mental health care records linked with maternity data, women with history of SMI who gave birth from 2007 to 2011 were identified. Relapse was defined as admission to acute care in the first 3 months postpartum. Women who were exposed to regular medication were compared with women who were unexposed. Data were analysed by pregnancy using random effects models to account for repeated measures in women who had more than one pregnancy in the study period.

Results: There were 452 full term pregnancies, of which 128 (28.3%) were associated with relapse in the first 3 months postpartum, with recent relapse an independent predictor (aOR; 95% CI:1.30–2.27). There was no evidence of a prophylactic effect of medication (crude OR = 0.65; 0.34–1.25) (aOR = 0.99; 0.54–1.83), in women with non-affective or affective psychoses (interaction test p = 0.453).

Conclusions: Recent relapse increases the risk of relapse in the postpartum period so women with severe illnesses with a recent history of relapse should be warned pre-conception about the high risk of relapse. The lack of evidence of a protective impact of medication prophylaxis may reflect confounding by indication.

1. Introduction

Relapse of serious mental illness (psychotic and bipolar disorders) around childbirth is potentially devastating. The acute onset of psychoses immediately following childbirth are among the most severe disorders seen in psychiatry and may be associated with adverse consequences for the woman, her family and the capacity to parent (Howard, 2005), as well as (rarely) lead to suicide and/or infanticide. UK and Australian Confidential Enquiries highlight psychiatric illness as a leading contributor to maternal deaths (Austin et al., 2007; Cantwell et al., 2011). Research has established that women with bipolar disorder have high risk of relapse postpartum, with reported estimates ranging from 17 to 75% (Di Florio et al., 2013; Doyle et al., 2011; Maina et al., 2014; Wesseloo et al., 2015). The first few weeks postpartum are the time of highest risk (Munk-Olsen et al., 2009)and primiparity (Di Florio et al., 2014), family history of bipolar disorder (Jones and Craddock, 2001, 2002), previous perinatal episodes (Chaudron and Pies, 2003) and not living with the father of the child have been highlighted as potential risk factors (Nager et al., 2005). Less research has been carried out in women with schizophrenia and other non-affective psychoses. Two large registry studies estimated 16–22% rates of readmission in the first 3 months postpartum (Harlow et al., 2007; Munk-Olsen et al., 2009) and more recently 19.1% for women with schizophrenia in the first year postpartum (Rochon-Terry et al., 2016). Previous inpatient admissions, the number and recency of previous admissions and admission during pregnancy have been associated with postpartum readmission in women with history of psychotic and bipolar disorders (Harlow et al., 2007; Munk-Olsen et al., 2009).

A recent systematic review reported that in women with bipolar disorder, postpartum relapse rates were significantly higher among those who were medication free during pregnancy (66%, 95% CI = 57, 75) than those exposed to medication (23%, 95% CI = 14, 37) (Wesseloo et al., 2015). However, in observational research it is very difficult to disentangle characteristics of the psychiatric illness from effects of

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medication and previous studies looking at medication and relapse have been limited in the potential confounding factors adjusted for. There has been no research looking at medication and postpartum relapse in women with schizophrenia.

We aimed to investigate risk factors for relapse of SMI (affective psychosis and non-affective psychoses) using a novel informatics case register of women in secondary mental health care in south London and examine whether medication exposure in the third trimester and early postpartum prevented relapse. We hypothesized that women on no medication in the third trimester of pregnancy and/or early postpartum would be at greater risk of postpartum relapse than women on regular medication in the third trimester and that women with history of affective disorders would be more likely to relapse than women with non-affective disorders.

2. Methods

2.1. Study design

Historical cohort study using secondary mental health care data linked to national maternity data.

2.2. Data source

The South London & Maudsley (SLAM) NHS trust provides secondary mental health care and some tertiary services including a perinatal service to a geographical catchment area of four London boroughs and a source population of around 1.2 million residents. Electronic records date back as far as 1999 and all clinical records have been fully electronic since 2006. The NIHR Biomedical Research Centre Clinical Record Interactive Search (CRIS) is an anonymised version of these used for research. There are about 250,000 patient records on the system and data can be retrieved from structured fields and free text (Perera et al., 2016). Much of the information is in free text and a number of natural language processing applications have been developed using General Architecture for Text Engineering (GATE) software, which allow structured data to be retrieved from free text taking into account the linguistic context of key search terms (Cunningham et al., 2013). CRIS has been approved as a research resource by Oxfordshire Research Ethics Committee C (08/H0606/71 + 5) and is linked to other sources of secondary data including Hospital Episode Statistics (HES). This is national statistical data for hospital admissions in England and includes maternity data (NHS Digital, 2016).

2.3. Study cohort

Methods to identify the study cohort are described elsewhere (Taylor et al., 2015). We included women with history of SMI who delivered babies from 2007 to 2011. CRIS was used to identify women with SMI and linked maternity HES to identify delivery of a baby (live birth or still birth over 24 weeks). Women with history of SMI before the pregnancy were included based on ICD-10 diagnoses F20, F22, F23, F25, F28, F29 (schizophrenia and related disorders, schizoaffective disorders and delusional disorders), F30, F31 (mania and bipolar affective disorders), F32.3, F33.3 (psychotic depression), or F53.1 (puerperal psychosis) from structured fields or a GATE diagnosis application. Where clear diagnostic history could not be ascertained or there was no available diagnostic data, notes were read by a researcher to determine the patient's psychiatric history from clinical notes. Women had to be under SLaM care at any point from 6 months before to 6 weeks after the HES delivery episode so that details of their mental health care during the perinatal period would be recorded. We excluded women with above diagnoses dated for the first time during or after pregnancy and women with insufficient data to establish medication use. Delivery date was ascertained from the last date of the HES episode or subtracting postnatal days of stay. Fig. 1 shows details of cohort, timelines and exclusions. We later added women who delivered babies from 2012 to 31st March 2013 when more HES data became available. Not all data were available for these extra pregnancies.

2.4. Measures

Relapse of SMI in first 3 months postpartum: admission to inpatient care or referral for home treatment/crisis resolution (services offered in the UK in an acute mental health crisis as an alternative to inpatient admission involving frequent (usually daily) home visits (Johnson et al., 2008). Data were extracted from structured fields in CRIS, supplemented by HES data for admissions to inpatient mental health wards outside SLaM. Admissions to the SLaM mother and baby unit can occur for acute psychiatric illness, prophylaxis or parenting assessments. Admissions for acute illness only were included.

Diagnosis at baseline, recorded just prior or at the start of pregnancy was categorised into non-affective (schizophrenia, delusional disorders, acute and transient psychoses, schizoaffective disorders, other non-organic psychoses) and affective SMI (bipolar affective disorder, psychotic depression and previous postpartum psychosis.). We also redefined acute and transient psychoses, schizoaffective disorders, other non-organic psychoses as possible affective psychoses. Unless otherwise stated, the original categorisation is used throughout.

Medication exposure: Regular antipsychotic, mood stabiliser or antidepressant exposure in third trimester and first week postpartum was ascertained using a GATE application supplemented by manual text searches. Stops, starts and switches in regular antipsychotics, mood stabilisers and antidepressants were noted. Possible non-exposure was categorised if there was a written concern about adherence indicating a possibility of no exposure. Starting a prophylactic medication was recorded in 3rd trimester or 1st week postpartum if a woman started a regular medication for reasons other than psychiatric symptoms. The GATE medication application has been validated for a number of antipsychotic medications with precision statistics ranging from 0.93–0.7 and recall from 0.57–0.92. Due to the time windows of medication required, documents identified by GATE were recalled and read manually for coding by researchers in order to establish a more 'gold standard' recording of medication in pregnancy. Two researchers rated medication exposure and a consecutive 22 cases were independently rated for identification of antipsychotic, mood stabiliser and antidepressant with agreement of 85%, 100% and 100% respectively for the third trimester of pregnancy.

2.4.1. Covariates

Ethnicity was extracted from structured data and categorised into 'Black African/Caribbean/other', 'White British/other', and 'Mixed, Asian, other/not stated'. Area-level deprivation score was extracted closest in date to beginning of pregnancy – a summary socioeconomic measure derived from UK Census data (2007) (Noble et al., 2007). Manual searches using piloted terms were carried out to establish children prior to index pregnancy, relationship status in pregnancy, history of childhood and domestic abuse (physical, sexual, emotional, and coercive) before or during pregnancy, smoking in pregnancy and family history of psychosis. We recorded and analysed positive hits only. If information is missing in the clinical text it is impossible to tell whether it is 'negative' or just not recorded. There was a very high proportion of missing information and information on 'negative' hits were not commonly reported. Therefore 'negative hits' and missing were combined. Covariates collected using manual free text searches were only for the original 2007–2011 cohort, not for pregnancies ending 2012–13.

Acute episodes were recorded if there was an admission to acute care (inpatient or home treatment) extracted using CRIS, supplemented with HES to identify admissions to inpatient care outside SLaM. We recorded acute psychiatric episodes during pregnancy and in the 2 years before. A spell of acute care in the 2 years before pregnancy was defined as a period of admission to acute mental health care where there was at

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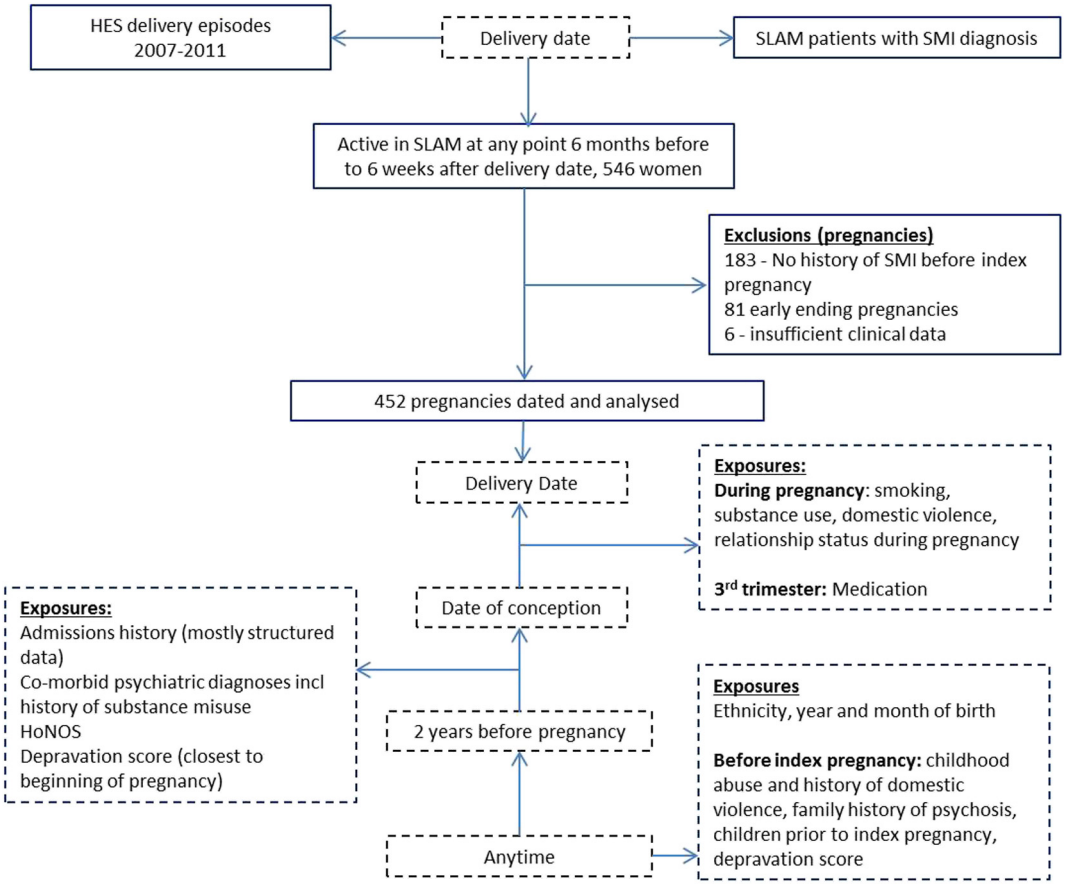

Fig. 1. Diagram to show how the cohort was established and exposure variables collected.

most 7 days between discharge and readmission. Recency of admission was coded 'pregnancy' if there was an admission during pregnancy and '1 year' if there was an admission in the year before pregnancy but not during pregnancy or '2 year' if the beginning of the most recent spell fell in the 2 years before the beginning of pregnancy. Fig. 1 displays time relationships of exposures and pregnancies.

Manual review of case notes was carried out to ascertain recorded smoking, and alcohol and drug use in pregnancy, supplemented by a substance misuse diagnosis within the previous 2 years. The highest total adjusted Health of the Nation Outcome Scale (HoNOS) score, a routinely collected 12 item measure in UK mental health services of health and social functioning of people with severe mental illness, recorded in the 2 years prior to delivery was also extracted (Wing et al., 1998). These data were only available for 2007–2011 pregnancies.

2.5. Data analysis

Data were analysed using STATA 12. Period prevalence of relapse in the first 3 months postpartum was calculated by pregnancy. Incidence of newly occurring relapses were then calculated excluding pregnancies where an acute admission occurred during pregnancy. Estimates were ascertained for the whole sample and separately for 1, 2 and 3 months postpartum and stratified by affective and non-affective SMI group. We also re-categorised possible affective disorders (schizoaffective disorder, acute and transient psychosis and psychosis NOS) in the affective group and then reported separately by 7 separate ICD-10 diagnoses at baseline (i.e. diagnosis closest to or at the start of the index pregnancy).

To account for repeated measures for women with more than one pregnancy in the cohort, random effects logistic regression were used to investigate crude associations between relapse and the two main exposures - and medication exposure and baseline diagnostic group. The same method was used to calculate associations between covariates and relapse, both including and excluding pregnancies where an acute admission occurred.

Multivariable analyses assessed association with medication in 3rd trimester and first week postpartum and relapse. Covariates were added as a two-stage process. The model was first adjusted for age and ethnicity and then other covariates were added which were associated with relapse at $p \leq 0.2$ (Bursac et al., 2008). To avoid collinearity, we used only 'recency of admission' (during pregnancy, 1 year or 2 years before) in the main analysis as it included adjustment for admission in pregnancy. Medication exposure was defined as exposure to regular antipsychotic, mood stabiliser and or antidepressant throughout. We also ran bivariate and multivariable analyses including pregnancies ending in 2012–2013 using covariates available including medication and those extracted from structured data.

Hypothesis driven interaction tests using the likelihood ratio were carried out. Given that women on no medication may be either more non-compliant or more psychiatrically stable, we ran a likelihood ratio test for the interaction of psychiatric stability (women who had not been admitted in the 2 years before pregnancy) and medication on relapse. Bipolar disorder has been associated with rapidly occurring postpartum relapse whereas non-affective diagnoses may represent a more chronic risk of relapse (Munk-Olsen et al., 2009) so we also ran a hypothesis test for the interaction of medication and diagnosis (affective vs non-affective) on relapse. Finally as domestic abuse may impact on symptomatology in women with SMI (Khalifeh et al., 2015) we ran a hypothesis driven interaction test for domestic abuse and medication.

Risk of relapse at 3 months postpartum in the affective and non-affective group were then compared using random effects logistic regression, adjusted for confounders. We also ran the model re-categorising possible affective disorders in the affective group and

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comparing schizophrenia and bipolar disorder only, in order to draw a comparison with literature looking only at bipolar disorder and schizophrenia.

2.5.1. Sensitivity analyses

Research has shown that admission in pregnancy is a predictor of postpartum relapse. However, admission, particularly if occurring in late pregnancy may be part of the same relapse. We therefore ran sensitivity analyses excluding pregnancies where admission occurred during pregnancy, both for comparison of relapse risk in the affective and non-affective groups, and analysis of medication and relapse. We used the same modelling strategy, but instead of using 'recency of admission', we adjusted for 'admission in 2 years before pregnancy' as there were fewer cases in these analyses and this measure of previous hospital admission was more strongly associated in the bivariate analyses excluding pregnancies with admissions. We also ran sensitivity analyses moving those who started a medication in the first week postpartum (for reasons other than emerging psychiatric symptoms) to the medication exposed group. To address possible misclassification of medication exposure, a sensitivity analysis excluded women coded as possibly non-adherent.

Due to research showing bipolar disorder to be associated with rapidly occurring postpartum relapse, further sensitivity analyses were carried out including relapses occurring in the first month postpartum only. These analyses were run including and excluding pregnancies with an admission during pregnancy and comparing affective and non-affective groups and schizophrenia and bipolar groups.

3. Results

3.1. Sample characteristics

The cohort included 452 pregnancies in 396 women (Fig. 1); 47 women had more than one pregnancy in the study period including 7 with more than two. At baseline, 200 (50.5%) had a diagnosis of non-affective SMI: 110 (27.8%) with schizophrenia or delusional disorder, 26 (6.6%) a schizoaffective diagnosis and 64 (16.2%) other non-affective diagnoses. The other 196 (49.5%) women had an affective SMI diagnosis including bipolar affective disorder (144 women, 36.4%), depressive psychosis (45 women, 11.4%) and 7 (1.8%) a history of postpartum psychosis only. Comorbid diagnoses between 9 months and 2 years before delivery included 18 (4.6%) women with substance use disorders, 9 (2.3%) with personality disorder diagnoses, 12 (3.1%) with anxiety disorders, 5 (1.3%) with learning difficulties and < 5 with other diagnoses including eating disorders, conduct disorders and epilepsy. There were 17 pregnancies with missing data for deprivation score and 186 pregnancies had missing HoNOS scores. Including pregnancies ending 2012–2013, there were 570 pregnancies in the cohort, 277 in the affective SMI group and 293 in the non–affective SMI group.

3.2. Medication exposures

In 3rd trimester, 274 (60.6%) pregnancies were exposed to regular medication; 234 (51.8%) to an antipsychotic, 30 (6.6%) to a mood stabiliser (19 (4.2%) to lithium) and 92 (20.35%) to an antidepressant. This includes 72 (15.9%) exposed to two medications and 18 (4.0%) to more than two. Five pregnancies had records of 'possible non-exposure' in the 3rd trimester. Of these 239 (87.2%) were also taking medication in the 2nd trimester and 88.7% (243) were also exposed in 1st trimester.

Of the 178 pregnancies unexposed to medication in 3rd trimester, 90.5% (n = 161) were also unexposed in 2nd trimester and 62.9% (n = 112) unexposed in the 1st trimester.

In 35 (7.7%) pregnancies there was initiation of regular medication (antipsychotic, mood stabiliser or antidepressant) in the 3rd trimester or 1st week postpartum for reasons other than emerging psychiatric symptoms. Of these, 24 had affective diagnoses and 11 non-affective. Of these also, 27 started a medication in the 1st week postpartum, 16 were not on medication in the 3rd trimester and 11 were.

By diagnosis (Suppl. Table 1), prevalence of medication exposure was a little higher in the non-affective group and schizophrenia group than the affective group. The most common medication group was antipsychotics and women with schizophrenia were about 50% more commonly exposed than women with bipolar disorder. However more (2–5 fold) of the bipolar group were on mood stabilisers compared with the non-affective groups. For antidepressants, exposure was around twice as common in the affective than non-affective groups.

3.3. Relapse in 3 months postpartum

There were 128 (28.3%) relapses during the first 3 months postpartum (see Fig. 2 for relapses by month and diagnosis). Most (71.1%) occurred in the first month and by the third month it was predominantly women with schizophrenia who relapsed. 89 (19.7%) pregnancies involved an admission to acute psychiatric care. Of these, 42 (47.2%) were also admitted in the first 3 months postpartum. For the 363 pregnancies without relapse during pregnancy, most postpartum relapses occurred in the first month. Women with broadly defined affective psychoses (i.e. affective psychoses, acute and transient, schizoaffective and psychosis NOS) were more likely to relapse earlier in the postpartum period. Including the pregnancies from 2012 to 2013, there were 151 (26.5%) relapses during the first 3 months postpartum (25.3% affective group, 27.7% non-affective). Excluding those who relapsed in pregnancy, there were 465 pregnancies, 105 (22.6%) with relapses postpartum (22.0% affective group, 23.2% non-affective).

3.4. Predictors of relapse in postpartum

Table 1 shows associations between covariates and relapse in the three months postpartum, both for the whole sample and excluding pregnancies with acute admission. Smoking and indicators of admission history were associated with relapse. Relapse in pregnancy was a strong predictor of relapse postpartum (OR: 5.09). Excluding those who relapsed in pregnancy, smoking, recency of admission and number of admissions in the two years before pregnancy were associated with relapse. Supplementary Table 2 shows analyses including 2012–2013 ending pregnancies. Results did not differ meaningfully.

3.4.1. Multivariable analysis

There was no association between medication exposure in 3rd trimester and relapse postpartum (Table 2). Stratifying by baseline diagnosis, the non-affective unexposed group had higher odds of relapse than those taking medication and the affective unexposed had lower odds of relapse than those on medication, but these were not significant. Likelihood ratio tests showed no evidence of an interaction between medication and baseline diagnosis on relapse (unadjusted chi2 = 0.20, p = 0.657, fully adjusted chi^2 = 0.56, p = 0.453), or between admission in the 2 years before pregnancy and medication on relapse (unadjusted chi2 = 0.01, p = 0.929, fully adjusted chi2 = 0.16, p = 0.685). Tests for interaction between history of domestic violence and medication (unadjusted chi2 = 1.81, p = 0.180, fully adjusted chi2 = 1.56, p = 0.212) and history of child abuse and medication (unadjusted chi2 = 0.69, p = 0.405, fully adjusted chi2 = 0.65, p = 0.421) on relapse suggested little evidence. Supplementary Table 3 shows unadjusted and fully adjusted odds of association with relapse for each covariate separately. In the fully adjusted model, recency of last episode was associated with relapse in 3 months postpartum. Table 3 compared relapse in the non-affective and affective groups. The non-affective groups had higher odds of relapse than the affective group, but findings were not significant and were attenuated on adjusting for confounders. When the affective/non-affective groups were re-categorised, the odds ratio of relapse in schizophrenia compared with the other diagnoses

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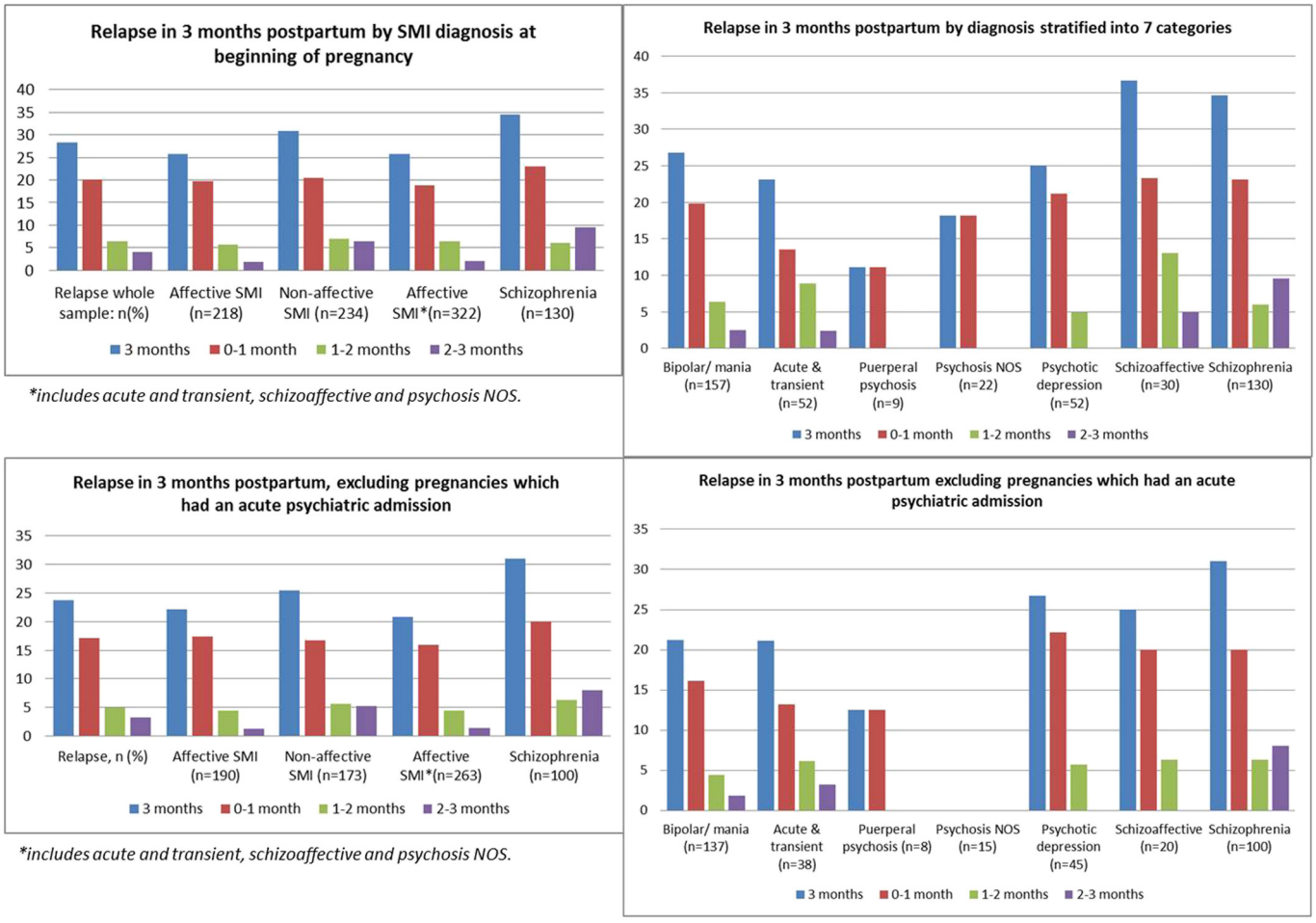

Fig. 2. Postpartum relapse by diagnosis at the beginning of pregnancy (numbers reflect pregnancy episodes rather than number of women).

was greater, and restricting to schizophrenia and bipolar disorder only, resulted in greater odds of relapse for schizophrenia compared with bipolar disorder although these differences were not statistically significant. Therefore, different ways of categorising the affective/non-affective group did not change our findings.

3.4.2. Sensitivity analyses

Although we did not find an association between medication in the 3rd trimester and relapse, excluding those who relapsed in pregnancy from the multivariable analyses further attenuated the findings such that odds ratios were closer to 1 and there was less difference between the medicated and unmedicated groups. Moving those who started prophylactic medication in the first week postpartum into the medication exposed group meant that the unexposed group were slightly more likely to relapse than the exposed group, but this did not change overall findings. Excluding those recorded as possibly non-exposed made little difference. There was a slight but non-significant attenuation in the association when excluding pregnancies where there was an admission to acute care in pregnancy (Table 2). Sensitivity analysis moving those who started medication in the first week postpartum increased the association slightly (making 'no medication' appear more protective) but non-significantly. Removing possible non-exposure to address misclassification of medication exposure made little difference to the findings.

For those who relapsed in first month postpartum (Table 4) findings were the same, although when stratified by SMI group, odds of relapse in the non-affective group were markedly attenuated compared with the full sample such that they went from having higher odds of relapse compared with the group on medication to lower odds of relapse. However, findings were not significant. Table 3 shows comparison of affective and non-affective disorders for pregnancies with relapses in the first month postpartum. Findings were the same as the full sample but odds were slightly attenuated.

4. Discussion

4.1. Main findings

In 389 women with history of SMI and 452 pregnancies from 2007 to 2011, there were 28.3% with a relapse in the first three months postpartum. After excluding pregnancies in which an acute psychiatric admission occurred, 23.7% had a relapse postpartum. Most were in the first month. Previous research has yielded a very wide range of estimates of risk of postpartum relapse particularly for women with bipolar disorder. However our findings are consistent with a recent meta-analysis of postpartum relapse in women with bipolar affective disorder and postpartum psychosis (Wesseloo et al., 2015). A recent population registry reported 19% (Rochon-Terry et al., 2016) were hospitalised in the first year postpartum in women with schizophrenia and found the first three months was the time of highest risk.

There was no association between medication exposure in pregnancy and relapse postpartum and sensitivity analysis including postpartum prophylaxis in the medication exposed group did not alter the findings. In contrast to our findings other literature has reported preventive effects of medication in pregnancy and the immediate postpartum on postpartum relapse. A systematic review reported pooled risk estimates of 23% in a total of 60 women with bipolar disorder exposed to medication in pregnancy compared with 66% in a total of 385

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Table 1
association of baseline diagnostic group, medication and covariates with relapse in first 3 months postpartum.

Covariates	All pregnancies (N = 452)				Excluding those who relapsed in pregnancy (N = 363)			
	N	% relapse	OR (CI)	P	N	% relapse	OR (CI)	P
No medication in 3rd trimester	178	24.7	0.65 (0.34,1.25)	0.199	168	23.8	1.00 (0.48,2.11)	0.994
Exposure to regular medication 3rd tri	274	30.7	Ref		195	23.6	Ref	
No medication in 3rd trimester	178	24.7	0.53 (0.27,1.03)	0.062	168	23.8	1.00 (0.48,2.11)	0.994
Exposure to regular medication 3rd tri or postpartum prophylaxis	274	30.7	Ref		195	23.6	Ref	
Baseline diagnosis								
Affective	218	25.7	Ref		190	22.1	Ref	
Non affective	234	30.8	1.41 (0.76,2.60)	0.234	173	25.4	1.33 (0.62,2.84)	0.463
Baseline diagnosis								
Affective (incl schizoaffective)	248	26.6	Ref		210	22.4	Ref	
Non affective	204	29.9	1.28 (0.70,2.37)	0.422	153	25.5	1.32 (0.61,2.85)	0.485
Ethnicity								
White	220	29.1	Ref		163	23.3	Ref	
Black	148	28.4	1.09 (0.54,2.21)	0.815	135	26.7	0.73 (0.31,1.72)	0.470
Asian/other	84	26.2	0.66 (0.25,1.75)	0.402	65	18.5	0.43 (0.13,1.48)	0.183
Deprivation score, median (range)	435	34.9 (4.8–61.5)	1.00(0.98,1.03)	0.745	349	34.9 (4.8–61.5)	1.00(0.96,1.03)	0.802
Age, mean (SD)	452	31.9 (6.0)	1.00 (0.96,1.06)	0.858	363	32.1 (6.0)	1.03 (0.96,1.03)	0.368
Partner during pregnancy	315	28.6	1.04 (0.54,2.00)	0.896	260	25.0	1.50 (0.63,3.59)	0.358
No partner during pregnancy	137	27.7	Ref		103	20.4	Ref	
Child abuse	93	36.6	1.80 (0.85,3.78)	0.123*	74	29.7	1.69 (0.67,4.27)	0.269
No child abuse	359	26.2	Ref		289	22.2	Ref	
DV before or during pregnancy	170	32.4	1.37 (0.74,2.53)	0.310	129	25.6	1.13 (0.52,2.45)	0.764
DV not reported	282	25.9	Ref		234	22.7	Ref	
Psychosis in 1st degree relatives	67	31.3	1.07 (0.45,2.53)	0.886	51	29.4	1.48 (0.53,4.15)	0.454
None recorded	385	27.5	Ref		312	22.8	Ref	
Primiparous	187	29.4	1.24 (0.67,2.28)	0.494	146	24.0	1.10 (0.52,2.32)	0.805
Not primiparous	265	27.6	Ref		217	23.5	Ref	
Preterm	68	19.1	0.47 (0.19,1.17)	0.105*	62	17.7	0.59 (0.21,1.64)	0.312
Full term	384	30.0	Ref		301	24.9	Ref	
Smoking in pregnancy	85	41.2	**2.52 (1.22,5.19)**	**0.013***	49	38.9	**3.30 (1.12,9.70)**	**0.030***
No smoking in pregnancy	367	25.3	**Ref**		314	21.4	**Ref**	
Harmful substance use	111	26.1	0.85 (0.42,1.69)	0.637	74	24.9	0.61 (0.23,1.59)	0.310
Not recorded	341	29.0	Ref		289	18.9	Ref	
Admission 2 years before pregnancy	191	35.6	**2.00 (1.16,3.47)**	**0.013***	136	30.2	**1.92 (0.95,3.9)**	0.068*
No admission 2 years before	261	23.0	**Ref**		227	19.8	**Ref**	
Admissions (N) before pregnancy								
0	261	23.0	Ref		227	19.8	Ref	
1	121	28.9	1.41 (0.76,2.59)	0.274	94	25.5	1.41 (0.66,3.03)	0.378
2	42	45.2	**2.94 (1.23,7.03)**	**0.015***	42	40.5	**3.50 (1.24,9.89)**	**0.018***
>/=3	28	50.0	**4.27 (1.44,12.68)**	**0.009***	–	–	–	–
Trend	*452*	*28.3*	***1.63 (1.21,2.20)***	***0.001****	*363*	*23.7*	***1.75 (1.09,2.83)***	***0.021****
Time since last episode								
None preg/2 y before	227	19.8	Ref		227	19.8	Ref	
2 years before	70	27.1	1.65 (0.70,3.89)	0.255	70	27.1	1.66 (0.70,3.90)	0.248
1 year before	66	33.3	2.15 (0.93,4.99)	0.073*	66	33.3	2.19 (0.95,5.03)	0.066*
Pregnancy	89	47.2	**5.96 (2.24,15.86)**	**<0.001***	*N/A*	*N/A*	*N/A*	*N/A*
Trend	*452*	*28.3*	***1.71 (1.30,2.27)***	***<0.001****	*363*	*23.7*	***1.49 (1.00,2.24)***	***<0.053****
Self-harm pregnancy/2 years before	86	30.2	1.23 (0.57,2.62)	0.597	46	15.2	0.33 (0.08,1.46)	0.146
No self-harm reported	355	27.9	Ref		317	24.9	Ref	
Highest HoNOS 6 2 years before delivery, median (range)	244	12 (0–29)	0.98 (0.90,1.06)	0.553	186	11 (0–29)	0.97 (0.90,1.04)	0.342

* $p < 0.2$.

women on no medication during pregnancy. However, a large proportion of the 'no medication' group came from one tertiary referral centre in a single clinical study of 276 medication free women (with a relapse rate of 75%), which may include women with particularly severe disorders; moreover, relapse was measured by medical note review from a clinician. There was also no adjustment in this meta-analysis for potential confounders. Previous research investigating medication in pregnancy and postpartum relapse in women with bipolar disorder has defined exposure across the whole of pregnancy (Bergink et al., 2012; Wesseloo et al., 2015). We instead focused on the third trimester as other research (Toh et al., 2013; Viguera et al., 2007) including our own work (Taylor et al., 2015) has shown that many women change medications in early pregnancy – over 40% of women in this cohort. In this cohort we have also found that women on no medication at the start of pregnancy tended to relapse early in pregnancy (Taylor et al., 2018), following which they are likely be commenced on medication. Given so many changes in medication in early pregnancy and consistency in medication groups particularly across 2nd and 3rd trimesters we thought later pregnancy would capture women who have been stabilised on medication following earlier changes coinciding with the commencement of pregnancy or secondary to relapse, although did not envisage that findings would be vastly different from those using data measuring exposure across the whole of pregnancy. However, it is also contrary to clinical observations that medication in pregnancy was not shown to be preventive for relapse. Our results might well reflect confounding by indication. Given that we used data from secondary mental health care it may be that women most at risk of relapse were managed well by secondary care services on medication than those who were less engaged. The groups were likely heterogeneous and although we attempted to look at some of the heterogeneity

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Table 2
Multivariable analyses of medication exposure and postpartum relapse in the first 3 months postpartum comparing those exposed to medication in 3rd trimester/first week postpartum (reference group) with those not exposed to medication.

All pregnancies	Whole sample (n = 452)	Moving starters (n = 452)	Excluding possible non-exposure (n = 447)
	OR (CI), p	OR (CI), p	OR (CI), p
Unadjusted association	0.65 (0.34,1.25), 0.199	0.53 (0.27,1.03), 0.062	0.65 (0.33,1.28), 0.211
Model 1*	0.63 (0.32,1.25), 0.189	0.50 (0.25,1.03), 0.059	0.63 (0.31,1.28), 0.202
Model 2†	0.99 (0.54,1.83), 0.975	0.76 (0.41,1.41), 0.380	0.98 (0.52,1.84), 0.943
Model 2	0.73 (0.22,2.48), 0.614	0.40 (0.09,1.68), 0.208 n = 218	0.73 (0.22,2.48), 0.614 n = 218
affective group	n = *218*		
Model 2	1.25 (0.63,2.45), 0.525 n = *234*	1.18 (0.61,2.30), 0.616 n = 234	1.21 (0.61,2.38), 0.583 n = 229
non-affective group			
Model 2	1.01 (0.37,2.89), 0.981N = 191	0.64 (0.22,1.89), 0.417	0.99 (0.36,2.74), 0.981
admitted 2 yrs before		N = 191	N = 189
Model 2	1.22 (0.18,8.29), 0.842	0.71 (0.10,4.90), 0.728	1.26 (0.19,8.29),0.810
not admitted 2 yrs before	N = 261	N = 261	N = 258
Model 2	0.59 (0.18,1.99), 0.398	0.33 (0.09,1.21), 0.095	0.58 (0.16,2.08), 0.402
History of DV	N = 170	N = 170	N = 168
Model 2	1.23 (0.64,2.35), 0.539	1.23 (0.64,2.37),0.540	1.23 (0.64,2.37), 0.525
no history of DV	N = 282	N = 282	N = 279
Model 2	1.28 (0.45,3.63), 0.649	1.29 (0.46,3.65), 0.632	0.89 (0.31,2.51), 0.649
History of child abuse	N = 93	N = 93	N = 93
Model 2	1.10 (0.42,2.90), 0.852	0.70 (0.26,1.91), 0.485	0.99 (0.32,3.07), 0.991
no history of child abuse	N = 359	N = 359	N = 354
Excluding acute admissions in pregnancy			
	(n = 363)	(n = 363)	(n = 361)
Unadjusted	1.00 (0.48,2.11), 0.994	0.81 (0.38,1.73), 0.581	0.98 (0.47,2.07), 0.963
Model 1*	1.07 (0.49,2.35), 0.868	0.83 (0.37,1.84), 0.645	1.05 (0.48,2.31), 0.901
Model 2†	1.05 (0.48,2.29), 0.897	0.93 (0.47,1.85), 0.836	1.17 (0.59,2.30), 0.658
Model 2	0.94 (0.36,2.44), 0.894 n = *190*	0.72 (0.26,2.00), 0.527 n = *190*	0.94 (0.36,2.44), 0.894 n = *190*
Affective group			
Model 2	1.47 (0.69,3.17), 0.320 n = *173*	1.29 (0.61,2.74), 0.502 n = *173*	1.41 (0.66,3.04), 0.376 n = *171*
Non-affective group			

*Model 1: adjusted for age & ethnicity.
†Model 2: Model 1, plus factors associated at p < 0.2 in Table 1 (preterm birth, history of child abuse, recency of last episode and smoking in pregnancy).

by examining interactions, the different secondary services, levels of care, severities of illness and engagement with professionals and medication regimes were not feasibly disentangled in a sample of this size.

No previous work has looked at the impact of medication on relapse in women with non-affective SMI in the perinatal period. Although discontinuation of medication is reported to be a major risk factor for relapse of schizophrenia outside of the perinatal period (Bassett et al., 1998; Vigod and Ross, 2010) women with schizophrenia who are pregnant may not be representative of women with schizophrenia in general.

4.2. Methodological considerations

There are many challenges in evaluating the impact of medication on prevention of relapse in the perinatal period in this type of observational study. Pregnancy may alter the pharmaco-kinetics of medications including increasing clearance of a number of medications and we were not able to define dose adjustments, therefore at least some women may have been undertreated in late pregnancy. Clinical records may under-report adherence and there will be heterogeneity in consistency of medication use, and illness characteristics – indeed, women on no medication may be particularly well and stable or chaotic and poorly engaged with services. However, removing those unwell in pregnancy (and therefore more likely to relapse postpartum) did not change our findings. In agreement with other data (Harlow et al., 2007; Munk-Olsen et al., 2009), we found that recency of last admission and admission in the 2 years before pregnancy were associated with postpartum relapse. Effect moderators not examined previously (e.g. non-affective psychosis, domestic violence and admission in the 2 years before pregnancy) did not suggest a significant impact on relapse but the study was underpowered to examine these interaction effects. As well as differences in relapse rates in women exposed and unexposed to medication,

Table 3
Random effects logistic regression analysis of relapse in first three months postpartum and the first month postpartum, comparing affective diagnosis at baseline (reference group) with non-affective diagnosis at baseline.

	Whole sample (n=452)	Recoding ICD-10 F23, F25, F28, F29 as affective (n=452)	Schizophrenia compared with bipolar (n=296)	Excluding relapses in pregnancy (n=363)
Non-affective diagnosis	OR (CI), p	OR (CI), p	OR (CI), p	OR (CI), p
Unadjusted	1.41 (0.76,2.60), 0.278	1.75 (0.91,3.37), 0.093	1.95 (0.79,4.84), 0.147	1.33 (0.62,2.84), 0.463
Model 1*	1.44 (0.75,2.76), 0.279	1.72 (0.88,3.38), 0.112	2.03 (0.78,5.25), 0.147	1.50 (0.65,3.46), 0.338
Model 2†	1.13 (0.62,2.05), 0.685	1.47 (0.79,2.75), 0.227	1.48 (0.61,3.62), 0.385	1.22 (0.59,2.50), 0.587
1st month relapses				
Unadjusted	1.08 (0.55,2.10), 0.823	1.38 (0.68,2.80), 0.373	1.47 (0.53,4.13), 0.459	0.97 (0.41,2.29), 0.946
Model 1*	1.08 (0.54,2.15), 0.837	1.34 (0.65,2.75), 0.423	1.53 (0.52,4.47), 0.438	1.06 (0.43,2.59), 0.906
Model 2†	0.90 (0.46,1.78), 0.764	1.18 (0.58,2.40), 0.644	1.20 (0.43,3.29), 0.728	0.94 (0.40,2.20), 0.886

* Model 1: adjusted for age & ethnicity.
† Model 2: Model 1, plus factors associated at p<0.2 in Table 1 (preterm birth, history of child abuse, recency of last episode and smoking in pregnancy).

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Table 4
Random effects logistic regression analysis of association with medication exposure and relapse in the first month postpartum.

All pregnancies	Whole sample (n = 452)	Excluding starters (n = 417)	Excluding possible non-exposure (n = 447)
	OR (CI), p	OR (CI), p	OR (CI), p
Unadjusted association	0.62 (0.30,1.27), 0.191	0.49 (0.23,1.04), 0.065	0.65 (0.33,1.28), 0.211
Model 1*	0.61 (0.29,1.28), 0.191	0.49 (0.23,1.04), 0.065	0.63 (0.31,1.28), 0.202
Model 2†	0.84 (0.41,1.72), 0.633	0.64 (0.31,1.33), 0.231	0.98 (0.52,1.84), 0.943
Model 2	0.74 (0.18,3.01), 0.670	0.70 (0.17,2.91), 0.624	0.74 (0.18,3.01), 0.670
affective group			
Model 2	0.88 (0.41,1.92), 0.749	0.59 (0.25,1.38), 0.221	0.85 (0.39,1.86), 0.693
non-affective group			
Excluding acute admissions in pregnancy			
	(n = 363)	(n = 333)	(n = 361)
Unadjusted	0.83 (0.35,1.98), 0.674	0.70 (0.29,1.69), 0.429	0.81 (0.34,1.95), 0.643
Model 1*	0.88 (0.36,2.16), 0.785	0.73 (0.30,1.79), 0.489	0.87 (0.35,2.12), 0.756
Model 2†	0.96 (0.41,2.22), 0.918	0.78 (0.33,1.80), 0.556	0.94 (0.41,2.19), 0.891
Model 2	0.77 (0.16,3.81), 0.751	0.55 (0.11,2.88), 0.479	0.77 (0.16,3.81), 0.751
Affective group	N = 190	N = 190	N = 190
Model 2	1.10 (0.46,2.64), 0.827	0.98 (0.42,2.32), 0.971	1.06 (0.44,2.55), 0.892
Non-affective group	N = 173	N = 173	N = 171

*Model 1: adjusted for age & ethnicity.
†Model 2: Model 1, plus factors associated at p < 0.2 in Table 1 (preterm birth, history of child abuse, recency of last episode and smoking in pregnancy).

women with non-affective disorders tended to have higher odds of relapse than women with affective disorders. Although not statistically significant, again the study might have had insufficient power to detect what might be a clinically significant difference. This study was initially powered to detect an odds ratio of 3.5 for relapse in pregnancy in women who discontinued versus those who continued medication in a sample size of 205.

These findings support current recommendations that decisions around medication in the perinatal period should involve a risk benefit analysis with attention to the likelihood of relapse based on individual circumstances, illness severity and recency of acute episodes (Jones et al., 2014). Clearly more evidence is needed on risks and potential benefits of medication in late pregnancy.

4.3. Strengths and limitations

A major strength of our study is the novel case register which has enabled us to look at a larger sample of women than would have been possible using a clinical study, while including clinical variables not available in administrative data. We were able to include women who may be too unwell to participate in clinical studies and our data is likely to be free of the selection and recall bias of retrospective studies which ascertain relapses by interview. Although we might have incurred some loss of data due to migration in this ethnically diverse population of South London, the additional use of HES to determine admission to inpatient care over the whole of England has enabled us to account for patients moving into and out of the catchment area, reducing loss to follow-up.

These data are likely generalisable to women managed in secondary care but we would not capture women managed in primary care who may be less severely ill, which may account for the slightly elevated rates particularly in the non-affective group in comparison with the population registries. However, given that the risk of relapse is thought to be at its highest in the early postpartum and the severe nature of these disorders, it is likely that a large majority of women would be managed in secondary care services at this time. The NICE guidelines recommend that women who have history of SMI are referred to secondary mental health care in the perinatal period (NICE, 2014). We were able to look at the whole heterogeneous spectrum of women with SMI managed in secondary care. It would have been useful to be able to determine the type of relapse and symptoms women with affective and non-affective SMI experienced. Use of HES enabled us to identify SLAM patients who delivered babies across the whole of England. Home births are thought to be not well recorded in HES and these account for 2.4% of births in England in 2007 (ONS, 2013). Again, women with SMI would be treated as high risk and therefore probably less likely to have home births than the general population.

Detailed clinical data available in the patient notes enabled us to capture medication use including definitive information about stopping and adherence, enabling us to reduce issues of misclassification bias. We were able to collect and adjust for information on many clinical and socio-demographic factors, which previous research has found to be associated with postpartum relapse. However, the CRIS data are not collected for research and rely on the comprehensiveness of the clinical notes which means that there is a strong likelihood of residual confounding due to information that is missing on variables such as smoking, drug use and acute relapses in previous perinatal periods which occurred more than 2 years before these index pregnancies.

4.4. Conclusions

This study confirms a high risk of relapse in the early postpartum period in women across the whole spectrum of SMI. However contrary to our hypothesis, women with affective disorders were not statistically more likely to relapse than women with non-affective disorders in this study. We did find that women with a recent relapse were at higher risk of postpartum relapse. Women with severe illnesses should be warned pre-conception about the risk of relapse, particularly if they have recently relapsed. Contrary to our hypothesis, women on no medication in the third trimester of pregnancy and/or early postpartum were not at greater risk of postpartum relapse than women on regular medication in the third trimester. The lack of (observational) evidence on medication prophylaxis here may well reflect confounding by indication and further research is needed on the risks and benefits of the different types of medication used for SMI in the perinatal period.

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Contributors

Taylor C carried out the analysis and wrote the draft manuscript. All authors were involved in design of the study and revised and approved the final version of the manuscript.

Conflict of interest

RS and MB have received research funding from Pfizer, Janssen, Lundbeck and Roche. RS supervises a PhD student funded by GSK.

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